REMARKS

A. Withdrawn Objections and Rejections

Applicants thank the Examiner for consideration of Applicants' Supplemental Amendment of June 13, 2011, following an interview with Applicants' representatives, Joseph D. Eng Jr. and Kenneth H. Sonnenfeld. Applicants also note with thanks the withdrawal of all previous objections to the specification and claims; as well as previous claim rejections for alleged indefiniteness and for alleged lack of novelty and/or obviousness based on U.S. Patent Application Publication No. 2004/0220100 to Waugh et al.; U.S. Patent Application Publication No. 2003/0229034 to Waugh et al.; and/or U.S. Patent No. 6,688,311 to Hanin. Action at pages 2-4.

B. Status of the Claims

Claims 1-50, 52, 56-63, 74-76, 118-145, and 147-148 have been cancelled previously. Claims 51, 79, 86, 87, and 93 are amended herein; claim 53 is cancelled; new claims 152-181 are added. Accordingly, with the entry of these amendments, claims 51, 54-55, 64-73, 77-117, 146, and 149-181 are pending. The amendments add no new matter, as discussed below.

Claims 51, 53-55, 64-73, 77-93, 97, 110, 149, and 150 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 78-80, 88, and 90-97 of co-pending U.S. Application No. 10/591,485. Action at pages 5-6.

Claims 51, 54, 55, 77 80-87, 97, 98, 149, and 150 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5, 10, and 11 of co-pending U.S. Application No. 12/647,677. Action at pages 6-7.

Claims 51, 53-55, 86-101, 110-115, and 151 are rejected under 35 U.S.C. § 102(b) for allegedly being anticipated by WO 02/07773 to Waugh et al. ("Waugh '773"). Action at pages 7-10.

Claims 51, 53-55, 64-73, 77-101, 109-117, 146, and 149-151 are rejected under 35 U.S.C. § 103(a) for allegedly being unpatentable over Waugh "773, in further view of U.S. Patent Application Publication No. 2011/0206731 to First ("First"). Action at pages 10-17.

Claims 102-108 are rejected under 35 U.S.C. § 103(a) for allegedly being unpatentable over Waugh "773, in further view of First and U.S. Patent No. 4,434,228 to Swann ("Swann"). Action at pages 17-19.

C. Explanation of the Amendments

Applicants have amended independent claim 51 to specify that the carrier of the claims is "a positively charged carrier comprising a positively charged polymeric backbone"; and that the botulinum toxin and the carrier form "a composition" where "the positively charged carrier and the botulinum toxin directly contact to form a non-covalent complex." Support for these amendments occurs in the specification, *e.g.*, at paragraph [0033], which provides that "[i]n all aspects of the present invention, the association between the carrier and the biologically active agent is by non-covalent interaction, non-limiting examples of which include ionic interactions, hydrogen bonding, van der Waals forces, or combinations thereof." Support also is found at paragraph [0048] of the specification, which refers to "toxin-carrier complexes". Still further support occurs at paragraph [0065], which states that the examples provided in the specification "demonstrate delivery of functional botulinum neurotoxin complexes across skin without requiring covalent modification of the neurotoxin to be delivered." Moreover, paragraph [0040]

specifically describes embodiments where "*only* a positively charged carrier that has positively charged branching groups is necessary for transdermal delivery of the botulinum toxin." (Emphasis added).

Claims 86, 87, and 93 merely are amended to include parentheses around the sequence identifiers recited in the respective claims.

Accordingly, Applicants respectfully submit that the claim amendments introduce no new matter. The same is true of the newly added claims.

New claims 152-179 are directed to various embodiments, where, *e.g.*, the polymeric backbone comprises polylysine, and where the polylysine is of various molecular weights. Support for these amendments can be found throughout the specification, *e.g.*, at paragraph [0042]. New claims 159, 166, and 173 further specify embodiments where at least one of the efficiency groups has "the formula $(gly)_p$-RKKRRQRRR-$(gly)_q$ (SEQ ID NO. 2) and the subscripts p and q are independently an integer in the range of 0 to 8"; or "the formula $(gly)_p$-YGRKKRRQRRR-$(gly)_q$ (SEQ ID NO. 3) and the subscripts p and q are independently an integer in the range of 0 to 8"; or "the formula $(gly)_p$-RKKRRQRRR-$(gly)_q$ (SEQ ID NO. 4) and the subscripts p and q are independently an integer in the range of 0 to 8", respectively. Support for these amendments occurs throughout the specification, *e.g.*, at paragraph [0037]. Claims 164-165, 171-172, and 178-179 further specify the botulinum toxin type, which aspects find support, *e.g.*, in paragraphs [0043] and [0010].

New claim 180 recites that "the efficiency groups attached to the polymeric backbone are present in an amount sufficient to enhance transdermal delivery of botulinum toxin relative to transdermal delivery of botulinum toxin using the same polymeric backbone but without attached efficiency groups". Support for this amendment can be found, *e.g.*, in Examples 1 and 2 of the

specification, which illustrate that transdermal delivery of botulinum toxin using the presently claimed carriers with attached efficiency groups is enhanced compared to positively charged carriers that lack such efficiency groups.

Finally, new claim 181 is directed to embodiments where the botulinum toxin comprises a fusion protein, support for which occurs in the specification, *e.g.*, at paragraphs [0043]-[0044].

Accordingly, Applicants respectfully submit that there are no issues of new matter with respect to the current amendments.

D. Alleged Obviousness-type Double Patenting

As noted above, the Examiner maintains the following two provisional non-statutory obviousness-type double patenting rejections:

- claims 51, 53-55, 64-73, 77-93, 97, 110, 149, and 150 over claims 78-80, 88, and 90-97 of co-pending U.S. Application No. 10/591,485 (Action at pages 5-6); and
- claims 51, 54, 55, 77 80-87, 97, 98, 149, and 150 over claims 1-5, 10, and 11 of co-pending U.S. Application No. 12/647,677 (Action at pages 6-7).

Applicants respectfully disagree. Further, Applicants again respectfully request that these rejections be held in abeyance, as none of the claims in the cited references or this case has been allowed as yet.

E. The Pending Claims are Novel over Waugh '773

Applicants respectfully traverse the rejection of claims 51, 53-55, 86-101, 110-115, and 151 under 35 U.S.C. § 102(b) for allegedly being anticipated by Waugh '773. Action at pages 7-10. Waugh '773 fails to disclose all of the features recited in Applicants' presently pending

claims. Accordingly, the rejection should be withdrawn. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987) (stating that claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference).

As amended, claim 51 reads as follows:

> 51. A method of administering botulinum toxin to a subject comprising
>
> topically applying to the skin or epithelium of the subject a composition comprising botulinum toxin and an effective amount of a positively charged carrier comprising a positively charged polymeric backbone having attached positively charged efficiency groups,
>
> wherein the botulinum toxin is not covalently modified, and
>
> wherein the positively charged carrier and the botulinum toxin directly contact to form a non-covalent complex.

As shown above, claim 51 requires that "the botulinum toxin is not covalently modified" and that "the positively charged carrier and the botulinum toxin directly contact to form a non-covalent complex." Waugh '773 does not disclose at least these two features, and therefore does not anticipate claim 51. *Verdegaal Bros* 814 F.2d at 631.

The present Office Action, however, contends that Waugh '773 anticipates the presently claimed invention, stating that

> Waugh et al. disclose a method of administering a botulinum toxin to a subject comprising topically applying to the skin or epithelium of the subject the botulinum toxin in conjunction with an effective amount of a carrier comprising a polymeric having attached positively charged efficiency groups, wherein the botulinum toxin is not covalently modified and wherein the carrier and the botulinum toxin non-covalently and directly associate.

Office Action at 9. To support this argument, the Office Action cites to the following sections of 'Waugh '773: Page 15, lines 20, 21, 26, 27, 33, and 34; page 17-lines 27-30, and page 19, lines 4-7. See Office Action, at 9.

None of these sections of Waugh '773 support the Office Action's position, however. The Office Action's position appears to be based on a reading of selected portions of the Waugh '773 reference without considering the context in which these disclosures were made. Applicants kindly ask the Examiner to consider the context of these disclosures, which Applicants discuss in the following paragraphs.

Waugh '773 is directed to the delivery of various classes of compounds, including imaging moieties, targeting agents, nucleic acids, persistence factors, and biological agents. *See, e.g.*, Waugh '773, p.3, lines 17-31. Under the "General" subheading in the "Description of the Invention" section, Waugh '773 states that "[t]he present invention provides a component-based system for selective, persistent, delivery of imaging agents, genes or other therapeutic agents. Waugh '773, p. 5, lines 16-17 (emphasis added). Waugh '773 further states that "therapeutic agents… are attached to a negatively charged backbone." Waugh '773, p. 17, lines 13-15. Figure 1 of Waugh '773 shows a schematic drawing illustrating a plurality of therapeutic agents as open circles attached to a negatively charged backbone. From at least these disclosures, a person of ordinary skill in the art would understand that a therapeutics agents are attached to a negatively charged backbone.

Waugh '773 further discloses that therapeutic agents include botulinum toxin. *See, e.g.*, Waugh '773, p. 16, line 14. In view of these combined teachings of Waugh '773 -- namely, that therapeutic agents are attached to ***negatively*** charged backbones and that botulinum toxin is a

therapeutic agent -- a person of ordinary skill in the art would understand that Waugh '773 requires botulinum toxin to be attached to a ***negatively*** charged backbone.

Furthermore, while Waugh '773 mentions that botulinum toxin can be a "cosmeceutical agent" as well as a "therapeutic agent" (*see, e.g.*, p. 15, line 34), Waugh '773 discloses that cosmeceutical agents are also attached to a negatively charged backbone. This can be seen, for example, in the following passage of Waugh '773:

> In one aspect, the present invention provides a composition comprising a non-covalent association complex of:
> a) a positively-charged backbone; and
> b) at least two members selected from:
> i) a first negatively-charged backbone having a plurality of attached imaging moieties;
> ii) a second negatively-charged backbone having a plurality of attached targeting agents;
> iii) at least one member selected from RNA, DNA, ribozymes, modified oligonucleotides and cDNA encoding a selected trans gene;
> iv) DNA encoding at least one persistence factor; and
> v) ***a third negatively-charged backbone having a plurality of attached biological agents***;
> wherein the association complex carries a net positive charge and at least one of the two members from group b) is selected from groups i), iii) or v).
> ***The biological agents, in this aspect of the invention, can be either a therapeutic agent or a cosmoceutic agent***.

Waugh '773, p. 3, lines 17-35. Further support is provided by the original claims of Waugh '773. More specifically, claim 1 of Waugh '773 requires "a third negatively-charged backbone having a plurality of attached biological agents" and corresponding dependent claim 4 specifies that the claimed "biological agent" is "a cosmeceutical agent." There is no specific disclosure or embodiment in Waugh '773 in which a "cosmeceutical agent" is used without covalently attaching it to a negatively charged backbone.

To summarize, Waugh '773 requires therapeutic agents, such as botulinum toxin, to be covalently attached to a negatively charged backbone. In view of this disclosure, Applicants

submit that the Office Action's citations to various passages in Waugh '773 do not support its contention that Waugh '773 anticipates Applicants' claims. For instance, the Office Action cites to lines 20, 21, 26, 27, 33, and 34 of page 15 of Waugh '773 as purportedly supporting its contention that Waugh '773 discloses that "botulinum toxin is not covalently modified," and that "the carrier and the botulinum toxin non-covalently and directly associate." However, the cited passages from page 15 of Waugh '773, which are highlighted in the passage below, merely discuss exemplary biological agents:

> ***biological agents***
>
> **A variety of biological agents, including both therapeutic** and cosmoceutic agents, are useful in the present invention and are present in an effective amount that will depend on the condition being treated, prophylactically or otherwise, the route of administration, the efficacy of the agent and patient's size and susceptibility to the treatment regimen.
>
> **Suitable therapeutic agents that can be attached to a negatively charged backbone can be found in essentially any class of agents, including, for example,** analgesic agents, anti-asthmatic agents, antibiotics, antidepressant agents, anti-diabetic agents, antifungal agents, antiemetics, antihypertensives, anti-impotence agents, anti-inflammatory agents, antineoplastic agents, anti-HIV agents, antiviral agents, anxiolytic agents, contraception agents, fertility agents, antithrombotic agents, prothrombotic agents, hormones, vaccines, immunosuppressive agents, vitamins and the like.
>
> **Suitable cosmeceutic agents include, for example, epidennal growth factor (EGF), as well as human growth hormone, antioxidants, and BOTOX.**

The Office Action's analysis fails to recognize that Waugh '773 discloses that when such biological agents are used, they are attached to a ***negatively*** charged backbone, as discussed above on pages 21-22 of this response.

The Office Action's references to page 17-lines 27-30, and page 19, lines 4-7 of Waugh '773 also do not support its § 102 rejection. The passage at page 17, lines 27-30 concerns nucleic acids, not botulinum toxin, as shown below:

> In yet another aspect, the present invention provides compositions comprising a non-covalent association complex of a positively-charged backbone having at least one attached efficiency group and at least one nucleic acid member selected from…

As the skilled artisan will appreciate, botulinum toxin is a protein comprised of a sequence of amino acids, whereas nucleic acids are not comprised of amino acids, are not proteins, and belong to a different class of biological molecules altogether. Similarly, the cited passage at page 19, lines 4-7, which is highlighted below, also does not discloses these claimed features:

> The pharmaceutical compositions of the invention preferably contain a vehicle which is pharmaceutically acceptable for an injectable formulation, in particular for direct injection into the desired **organ, or for topical administration (to skin and/or mucous membrane). They may in particular be sterile, isotonic solutions or dry compositions, in particular freeze-dried compositions, which, by addition, depending on the case, of sterilized water or of physiological saline, allow injectable solutions to be made up.** For example, the doses of nucleic acid used for the injection and the number of administrations may be adapted according to various parameters, and in particular according to the mode of administration used, the pathology concerned, the gene to be expressed, or alternatively the desired duration of the treatment.

Moreover, Applicants point out that the passage on page 19 of Waugh '773 cited by the Office Action is directed to ***injectable*** formulations, whereas claims currently at issue in this case are directed to a method of administering botulinum toxin by ***topically applying*** a botulinum toxin-containing composition. For all of these reasons, Applicants respectfully submit that the cited passage on page 19 of Waugh '773 is not applicable to the presently pending claims and do not anticipate the presently claimed invention.

The Office Action's analysis is also improper because it appears to conflate "positively charged backbones" with "negatively charged backbones." According to the Office Action,

> Waugh et al. do not specifically disclose that the botulinum toxin is required to be covalently attached to a ***negatively charged*** backbone as Applicant argues. Further, Waugh does not exclude the biological agent, in this instance Botox, from having a ***positively charged backbone*** present. In fact, Waugh et al. specifically disclose that the present invention provides compositions comprising a non-covalent association complex of a positively charged backbone having at least one attached efficiency group and at least one nucleic acid member (see page 17, lines 27-30).

Office Action at 10 (emphasis added). With respect to the first statement, Waugh '773 discloses that botulinum toxin is a therapeutic agent and that therapeutic agents are attached to negatively charged backbones, as discussed above. With respect to the second point, whether Waugh '773 reports the use of a ***positively charged*** backbone is not relevant to Applicants' arguments that Waugh '773 is distinguishable from the present invention because Waugh '773 requires covalent attachment of a ***negatively*** charged backbone to a therapeutic agent (e.g., botulinum toxin). Thus, the Office Action's analysis regarding "positively charged backbones" does not support any contention that Waugh '773 meets the requirement that "the botulinum toxin is not covalently modified." Finally, the Office Action argues that "botulinum toxin is equivalent to insulin," stating that

> while Example 4 pertains to insulin, Waugh specifically discloses that in the most preferred embodiment, the biological agent is selected from insulin, botulinum toxin a 4 others. Consequently, botulinum toxin is equivalent to insulin and the specification teaches specific modifications to biological agents, which are identical to those limitations of the claimed invention.

Office Action, at 10. The Office Action's focus on "specific modifications to biological agents" misses the point that the present claims require that "the botulinum toxin is ***not*** covalently modified." Thus, the covalent modifications to insulin and other biological agents disclosed in

Waugh '773 do not read on or anticipate the presently claimed invention, which requires a "botulinum toxin" that is "***not*** covalently modified."

F. The Pending Clams are Not Obvious over the Cited References

Applicants respectfully traverse the rejection of claims 51, 53-55, 64-73, 77-101, 109-117, 146, and 149-151 under 35 U.S.C. § 103(a) for allegedly being unpatentable over Waugh '773 in further view of First; as well as the rejection of claims 102-108 under 35 U.S.C. § 103(a) for allegedly being unpatentable over Waugh '773, in further view of First and Swann. Office Action at pages 10-19. To establish *prima facie* obviousness of a claimed invention, all claim limitations must be taught or suggested by the prior art. See, e.g., *In re Royka*, 490 F.2d 981, 985 (CCPA 1974). The Office Action does not meet this burden.

Waugh '773, as discussed above, fails to teach or suggest all of the features recited in Applicants' presently pending claims. For instance, Waugh '773 fails to teach or suggest a "method of administering botulinum toxin" involving "topically applying to the skin or epithelium" a "composition comprising botulinum toxin and an effective amount of a positively charged carrier…***wherein the botulinum toxin is not covalently modified***, and wherein ***the positively charged carrier and the botulinum toxin directly contact to form a non-covalent complex***."

First does not provide these missing features. To the extent that First mentions topical administration of botulinum toxin, First does not teach or suggest combining the "botulinum toxin [that] is not covalently modified" with the "positively charged carrier" recited in the presently pending claims. Thus, the combination of Waugh '773 and First does not teach or suggest the "method of administering botulinum toxin" as required by claim 51, the only pending

independent claim in this case. Accordingly, claim 51 and corresponding dependent claims 51, 53-55, 64-73, 77-101, 109-117, 146, and 149-151 are patentable over the combination of Waugh '773 and First.

Moreover, dependent claims 102-108 are patentable over the combination of Waugh '773, First, and Swann. Like Waugh '773 and First, Swann does not teach or suggest a "method of administering botulinum toxin" involving "topically applying to the skin or epithelium" a "composition comprising botulinum toxin and an effective amount of a positively charged carrier…wherein the botulinum toxin is not covalently modified, and wherein the positively charged carrier and the botulinum toxin directly contact to form a non-covalent–complex" as required by these claims. If anything, Swann actually teaches away from the method of administration recited in claims 102-108, because it is directed to ***immobilization*** of biological materials in condensed polyalkyleneimine polymers, rather than "a method of administration."

In sum, the cited combinations of Waugh '773, First, and Swann fail to teach or suggest all of the features of the pending claims. Accordingly, Applicants respectfully maintain that the pending claims are patentable over Waugh '773, First, and Swann, regardless of whether they are considered alone, in combination, or in sub-combination.

CONCLUSION

Based on the foregoing amendments and remarks, Applicants respectfully request reconsideration and withdrawal of all outstanding claim rejections and allowance of this application.

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this amendment and response to Deposit Account No. 50-3732, Order No. 13720-105071US2.

In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. 50-3732, Order No. 13720-105071US2.

Respectfully submitted,
KING & SPALDING, L.L.P.

Dated: March 15, 2012

By: /Joseph D. Eng Jr./
Joseph D. Eng Jr./Kenneth H. Sonnenfeld
Registration Nos. 54,084/ 33,285

Correspondence Address:
King & Spalding LLP
1185 Avenue of the Americas
(212) 827 - 4318 Telephone
(212) 556 - 2222 Facsimile